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Review of Epidemiologic Study Results of Vinyl Chloride-Related Compounds

by Rosanne Apfeldorf* and Peter F. Infante*

Epidemiologic study results addressing the carcinogenicity of six compounds related to vinyl chloride (vinylidene chloride, trichloroethylene, perchloroethylene, carbon tetrachloride, ethylene dibromide and epichlorohydrin) are reviewed.

The study results suggest an increased carcinogenic risk among workers exposed to epichlorohydrin and to dry cleaning and degreasing solvents. Although several studies report no significant excess of cancer mortality, an evaluation of the design of these investigations demonstrates that these negative cohort studies consisted of populations of insufficient sample size and latency to permit any meaningful conclusions regarding carcinogenic risk. Therefore, experimental studies must be relied upon to determine whether several of these substances pose a potential carcinogenic risk to humans. Available evidence indicates that all of these substances have demonstrated a carcinogenic response in experimental animals and most are mutagenic in experimental test systems.

Introduction

In the early 1970's, bioassays demonstrated the induction of cancer at multiple sites in experimental animals exposed to vinyl chloride (VC) by several routes of administration. Subsequently, epidemiologic studies confirmed an excess cancer risk of multiple sites among individuals employed in operations using VC (*1*). As a result of these observations, attention was focused on the toxicity of structural analogs of vinyl chloride. This review will present information on the potential for human exposure and the carcinogenic risks associated with exposure to these substances.

Magnitude of Exposure

Studies of occupational groups exposed to six VC-related substances have been conducted. Estimates of the annual production, number of worker exposures derived from 1972-74 National Occupational Hazard Survey data and current OSHA permissible exposure limits expressed as 8-hr time-weighted averages (TWA), for levels of occupational exposure to these substances are presented in Table 1. These substances are produced in high volume, and exposures involve large numbers of workers. As some of these substances were not produced in relatively high volume until the 1950's (*2*), the latency period required for the statistically sensitive evaluation of any potential cancer risk in the exposed individuals has not yet been achieved for a large proportion of exposed individuals.

Table 2 presents occupations and industrial uses for six substances structurally or industrially related to VC. Epichlorohydrin (ECH) is used in the manufacture of epoxy resins and has been used as a chemical stabilizer in trichloroethylene (TCE) and in plastics. Vinylidene chloride (VDC) is used in the manufacture of copolymers and fibers. Ethylene dibromide (EDB) is used in the manufacture of petroleum products and as a pesticide. TCE, perchloroethylene (PCE) and carbon tetrachloride (CCl_4) are used in metal degreasing operations. Although TCE and CCl_4 have been used as dry cleaning solvents in the past, PCE is the major dry cleaning solvent in use today.

Experimental evidence now demonstrates that many of the compounds structurally and industri-

*Office of Carcinogen Identification and Classification, Health Standards Programs, Occupational Safety and Health Administration, U.S. Department of Labor, Washington, D.C. 20210. The opinions expressed in this paper reflect those of the authors and are not necessarily those of the Occupational Safety and Health Administration.

ally related to vinyl chloride are carcinogenic (*3*). Many of these substances are also mutagenic (*4*, *5*). Bioassay study results have demonstrated the induction of tumors at multiple sites as a result of exposure to EDB and CCI_4. Cancers of the respiratory tract have been induced in experimental animals exposed to EDB and ECH. Liver cancers have been induced in animals exposed to VDC and EDB as well as to the industrial solvents TCE, PCE and CCl_4.

While these experimental studies were being conducted, the Interagency Regulatory Liaison Group (IRLG) was drafting documentation guidelines for epidemiologic studies (*6*). Also during this time, hearings on OSHA's cancer policy were proceeding, with much emphasis given to the role of nonpositive epidemiologic studies in qualitative risk assessment. The epidemiologic considerations, expressed in the IRLG guidelines and discussed in the OSHA cancer policy (*7*) will be used in this paper to assess the methodology and results of several epidemiologic studies of populations potentially exposed to one or more of the structural analogs of vinyl chloride.

Epidemiologic Study Results

A study of workers exposed to ECH was reported by Enterline in 1978 (*8*). These data were analyzed by using the NIOSH life table program (*9*) and are presented in the summary data table (Table 3). Members of the cohort were employed for more than one quarter of a year any time between 1948 to 1966, and followed through the end of 1977. Expected numbers of deaths were based on U.S. age, sex, race and calendar time-period specific rates. Ninety-four percent of the employees had achieved a minimum of 15 years of latency. Fifty-one deaths from all causes were observed, and 82 were expected. Thirteen deaths due to cancer were observed compared to 14.2 expected. Though not statistically significant, a doubling of the lung cancer risk was observed among individuals who had achieved a latency period of at least 15 years since first exposure to ECH. For the entire cohort, eight lung cancers were observed when 4.9 were expected. These data suggest that workers exposed to ECH may be at an increased risk of lung cancer, but further follow-up is necessary to in order to achieve

Table 1. Estimates of U.S. annual production, number of worker exposures, and OSHA time-weighted averages for VC and structural analogs.

Carcinogenic substance	Annual U.S. production, lb × 10[a]	Estimated number of worker exposures	OSHA TWA, ppm[b]
Epichlorohydrin (ECH)	220[c]	85,000	5
Vinylidene chloride (VDC)	200[d]	6,500–58,000	None
Trichloroethylene (TCE)	300[c]	282,000	100
Perchloroethylene (PCE)	770[e]	500,000	100
Carbon tetrachloride (CCl_4)	704[e]	160,000–2,000,000	10
Ethylene dibromide (EDB)	230[c]	9,000–660,000	20
Vinyl chloride (VC)	7544[e]	27,000–2,200,000	1

[a]International Trade Commission estimates.
[b]TWA = 8-hr time-weighted average.
[c]1978 estimates.
[d]Year not available.
[e]1979 etimates.

Table 2. Industrial uses and potential occupations with exposure to six carcinogenic substances.

Substance[a]	Major uses	Major occupational exposure industries
ECH	Manufacture of epoxy resins, surface active agents, and other chemicals	Assemblers, machinists, painters, chemical workers
VDC	Manufacture of copolymers and modacrylic fibers	Chemical workers, plastics workers
TCE	Metal degreasing, organic solvent	Chemical workers, metal workers, textile processing
PCE	Drv cleaning and textiles, metal cleaning, chemical manufacturing	Dry cleaners, chemical workers, textile workers, metal workers
CCl_4	Chemical manufacturing, grain fumigation, organic solvent	Chemical workers, grain fumigators
EDB	Fumigant, fuel additive, organic solvent	Chemical workers, petroleum products, exterminators and fumigators

[a]See Table 1.

a more sensitive estimate of the carcinogenic risk in humans. Several factors should be considered in evaluating these data. Some cohort members had been employed in the manufacture of isopropyl alcohol (IPA). This process has been associated with nasal sinus cancer, but the data to date have not demonstrated an excess of lung cancer among workers employed in the manufacture of IPA. In addition, the size of the cohort was small, and the average age of the cohort members during the followup period was only 48 years. The young age of the cohort is reflected in the low SMR of 63 for the entire cohort. Nevertheless, the data appear to be consistent with results of experimental bioassay which demonstrate ECH-induced cancers of the respiratory system.

Shellenberger et al. (*10*) reported on the mortality experience of 553 white male employees potentially exposed to ECH for at least one month between October 1957 and November 1976. Expected numbers of deaths were based on death rates for the Texas white male population for 1960 and 1970. Cause-specific observed and expected deaths and standardized mortality ratios for the entire cohort and for a subcohort employed in at least one job with a TWA of greater than 1 ppm were calculated. Twelve deaths were observed among cohort members, compared to 20.7 expected. No specific cause of death was in excess. Only two cancer deaths were observed compared to 3.5 expected. This cohort has not been observed for a long enough time period, as only 13% of the cohort had a latency of 15 or more years since employment.

Ott et al. (*11*) reported on the mortality experience of 138 employees exposed to VDC at any time between 1942 and 1968 and followed through 1973. Mortality among the exposed group was compared to the expected based on U.S. white male mortality rates. Five deaths were observed, compared to 7.5 expected. Only one cancer death was observed, compared to 1.1 expected. Clearly, the sample size is too small to allow any meaningful conclusion.

Axelson et al. (*12*) reported on the mortality experience of 518 male workers exposed to TCE in the 1950's and 1960's and followed through 1975. Eleven deaths from cancer occurred in the total cohort when 14.5 were expected. Among the subcohort who had achieved at least 10 years since first exposure, 9 deaths from all cancers were observed compared to 9.5 expected. The number of deaths from tumors are too small to analyze by site specific risk.

Table 3. Observed and expected deaths from studies of workers exposed to selected halogenated hydrocarbons.

Substance	Study	Total deaths			Total cancer deaths			Site-specific cancer deaths			
		Obs.	Exp.	SMR	Obs.	Exp.	SMR	Site	Obs.	Exp.	SMR
ECH	Enterline (*8*)	51	81.7	63	13	14.2	92	Respiratory	8	5.2	154
	Brown and Rinsky (*9*)							Lung	8	4.9	163
								Digestive	2	3.4	58
								Lymphatic	2	1.9	103
	Subcohort ≥ 15 yr latency	33	44.6	74	12	8.9	135	Lung	7	3.5	200
ECH	Shellenberger (*10*)	12	20.7	58	2	3.5	57				
VDC	Ott (*11*)	5	7.5	67	1	1.1	91	Respiratory	1	0.3	333
	Subcohort, ≥ 15 yr latency	2	2.6	77	1	0.5	200	Respiratory	1	0.2	500
TCE	Axelson (*12*)	49	62.0	79	11	14.5	76				
	Subcohort ≥ 10 yr latency, high exposure	8	7.6	105	3	1.8	167				
EDB	Ott (*15*)	36	32.5	111	7	5.8	121				
	Subcohort ≥ 15 yr latency	26	21.8	119	6	4.3	140				
TCE	Blair (*13*)[a]	330	330	–	87	67.9	1.28	Lung bronchus	17	10.0	1.7
PCE								Cervix uteri	10	4.8	2.1
CCl_4								Kidney	2	1.0	2.0
								Skin	3	0.7	4.3
								Leukemia	5	2.2	2.3
								Digestive	25	18.0	1.4
TCE	Blair (*14*)[a]	1292	1292	–	244	223.7	1.09	Esophagus	10	5.4	1.9
								Liver	10	6.1	1.6
								Lung	62	58.7	1.1
								Digestive	86	72.6	1.2

[a]Relative risk.

Mortality patterns among dry cleaning and laundry workers, potentially exposed to CCl_4, TCE, PCE and petroleum solvents, were studied by Blair et al. (*13*) and analyzed by the proportionate mortality method. The age-, race- and sex-specific cause of deaths for persons in the U.S. between 1957 and 1970 served as the comparison. A significant excess of cancer mortality was observed, with 87 cancer deaths observed and 67.9 expected. Malignancies of the respiratory system, skin and uterine cervix were significantly elevated. Because these workers were exposed to multiple substances known to be carcinogenic, it is difficult to attribute this excess to one substance.

Blair (*14*) recently reported the results of a proportionate mortality study of workers in the metal polishing and plating industry. These workers were potentially exposed to various metals, corrosive and caustic alkaline solutions, and solvents such as TCE and PCE. Mortality patterns among white male metal platers who died between 1951 and 1969 were compared with expected numbers based on cause-specific proportionate mortality for U.S. white males. Excess cancers of the esophagus and liver were present in the study population. Excess cancers of other organs, such as lung and digestive system, were not statistically significant. As with the dry cleaner population, exposures to more than one substance known to induce cancer experimentally do not allow the determination of any specific etiologic factor.

Ott et al. (*15*) reported on the mortality experience of 161 men exposed to EDB. Expected deaths were calculated from the U.S. white male general population. No excess of total deaths or total malignancies occurred. Of the total cohort, 86% achieved a latency of at least 15 years since first exposure. The number of cancer deaths in this study is too small to permit any valid inferences regarding the carcinogenic risk of the EDB exposed workers.

Of the substances reviewed, only the studies of workers exposed to ECH and to dry cleaning and degreasing solvents suggest an elevated risk of cancer. The excess liver cancer in the studies by Blair et al. (*13*, *14*) is noteworthy in view of experimental study results demonstrating the induction of liver cancer with the same industrial solvents to which these workers were exposed. The remaining studies report no significant excess of cancer mortality. However, it is apparent that each of these "negative" cohort studies did not consist of a sufficient sample size and latency period to permit any meaningful conclusion regarding carcinogenic risk. The probability of identifying an excess cancer risk in the study population, if in fact it is present, is referred to as the power of the study. The power for the cohort studies reviewed was calculated based on the methods of Cutler et al. (*16*) and Beaumont and Breslow (*17*). Table 4 shows the

Table 4. Observed and expected numbers of cancer death latency, minimum number of cancer deaths needed to insure statistical significance at the 0.05 level (one tailed-test) and the statistical power to detect a 1.5 relative risk.

Substance	Investigators	Site of cancer	Observed deaths	Expected no. of deaths at comparison population rate	Minimum no. of deaths required to conclude that study population rate exceeds comparison population rate[a]	Probability of concluding that study population rate exceeds comparison population rate when it is actually 1.5 times as high (power)[b]
ECH	Enterline (*8*),	All cancer	13	14.15	22	0.52
	Brown and Rinsky	Lung cancer	8	4.92	10	0.26
	(*9*) Greater than	All cancer	12	8.92	15	0.38
	15 yr latency	Lung cancer	7	3.48	8	0.21
ECH	Shellenberger (*10*)	All cancer	2	3.50	8	0.21
VDC	Ott (*11*)	All cancer	1	1.1	4	0.12
	Greater than 15 yr latency	All cancer	1	0.5	3	0.09
TCE	Axelson (*12*)	All cancer	11	14.5	22	0.53
	Greater than 10 yr latency	All cancer	9	9.5	16	0.40
EDB	Ott (*15*)	All cancer	7	5.8	11	0.29
	Greater than 15 yr latency	All cancer	6	4.3	9	0.24

[a]If the minimum number of cases is observed, the probability of incorrectly concluding that the study population rate exceeds the comparison population rate, when in fact it does not, is less than 0.05.

[b]Calculated as: $Z^{(1-\beta)} = 2n^{1/2}(R^{1/2} - 1) - Z^{\alpha}$, where R = relative risk, Z^{α} = upper 100α percentile of unit normal distribution, $Z^{(1-\beta)}$ = upper $100(1-\beta)$ percentile of unit normal distribution, and n = expected number of cases.

observed and expected number of total cancer of lung cancer deaths, the minimum number of deaths needed to observe the respective significant excesses and the resultant power to identify a 50% increase in the risk. The data are calculated for the total cohorts and the subcohorts with 10 or more or 15 or more years since initial exposure, as indicated in the studies. In order to conclude that the rate of cancer in the study population is greater than the rate of cancer in the control population, the number of observed cancer deaths must equal or exceed the minimum number of deaths required, as calculated using the Poisson distribution. The power calculations were based on the ability to detect an increase of 50% in the overall cancer risk of the study population, i.e., a relative risk of 1.5. [Criteria established by OSHA (*7*) for adequate sensitivity and specificity of an epidemiologic study require the ability to detect a relative risk of 1.5 in site-specific cancer risk.] The power of each study was determined by using the expected number of cancer deaths generated by the respective comparison population rate. The power to detect a 50% increase in total cancer mortality for the entire cohort ranges from 0.12, as shown for the VDC study of Ott et al., (*11*) to 0.52 for the Enterline study of ECH (*8*) and 0.53 for the Axelson study of TCE (*12*). These calculations clearly illustrate that the probability of detecting a 50% increase in total cancer mortality was rather low. For the cohorts with 10 or more or 15 or more years of latency, the power to detect a difference is even less. If the more appropriate site-specific cancer risk is considered, the statistical power to detect a difference is still lower. These latter data are not presented.

Further calculations from data in Table 3 illustrate the site-specific insensitivity of these studies. Given the expectation of 0.2 respiratory cancer deaths as reported in the VDC analysis (*11*), an observed risk of tenfold would be required to achieve statistical significance. However, this would still be based on only two deaths from a common malignancy. Axelson et al. (*10*) outlined several limitations of their analysis of workers exposed to TCE. A twofold risk of total cancer mortality would have been required to demonstrate a statistically significant excess in their study population, the magnitude of which is rarely observed in cohort mortality studies. The authors concluded that "the cancer risk to man from TCE can by no means be ruled out from this study, particularly with regard to uncommon malignancies such as liver cancer." The authors further stated that had one case of liver cancer been observed, the relative risk for cancer at this site would have been 3.4 for the total cohort and 25.0 for the high exposure subcohort. As stated by OSHA (*7*), the group of exposed subjects must be large enough to permit detection at least a 50% increase in site-specific cancer incidence in comparison to the control population. Cohort mortality studies such as these do not meet these criteria and therefore lack the sensitivity and specificity to detect an excessive cancer risk.

Conclusion

Although experimental studies have now demonstrated the carcinogenicity and mutagenicity of VC related compounds, in general, epidemiologic studies available for review do not allow for the assessment of carcinogenic risk among humans exposed to these substances. This conclusion is based on the observation that all of the cohort studies reviewed lacked sufficient statistical power because of the small sample sizes. Furthermore, individuals were not followed over an adequate period of time to allow cancers to become clinically manifest.

Although information presented indicates that all of the substances studied are high production volume chemicals with large estimated numbers of exposed workers, the number of workers available for study who have achieved an adequate latency period is small. The retention of personnel records containing the information necessary for epidemiologic study of health hazards is not a requirement in the United States and adds to the problem of insufficient sample sizes available for study. On the basis of these observations, it is apparent that qualitative carcinogenic risk of a specific chemical substance to humans must be estimated through the conduct of experimental studies.

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